חוק הפטנטים, תשכ"ז — 1967
PATENT LAW, 5727 - 1967

# בקשה לפטנט
Application for Patent

לשימוש הלשכה
For Office Use

| | |
|---|---|
| מספר: Number | 109656 |
| תאריך: Date | 1 5 -05- 1994 |
| הוקדם/נדחה Ante/Post-dated | |

אני, (שם המבקש, מענו ולגבי גוף מאוגד - מקום התאגדותו)
I (Name and address of applicant, and in case of body corporate-place of incorporation)

כמאגיס בע"מ
חברה ישראלית,
רח' לח"י 29
בני ברק 51200

CHEMAGIS LTD.,
an Israeli company, of
29 Lehi Street
Bnei Brak

הממציא: סטפן צ'רקז

Inventor: Stephen Cherkez

בעל אמצאה מכח ..... הדין ..... ששמה הוא .....
Owner, by virtue of ..... of an invention the title of which is .....

(בעברית) (Hebrew)
תהליך לייצור אנדרוסטיין-17-קרבוטיואטים
ואנדרוסטיין-17-קרבוטיואטים המיוצרים ע"י התהליך האמור

(באנגלית) (English)
PROCESS FOR THE MANUFACTURE OF ANDROSTANE-17-CARBOTHIOATES AND ANDROSTANE-17-CARBOTHIOATES PREPARED THEREBY

מבקש בזאת כי ינתן לי עליה פטנט
hereby apply for a patent to be granted to me in respect thereof.

| • בקשת חלוקה — Application of Division | • בקשת פטנט מוסף — Application for Patent Addition |
|---|---|
| מבקשת פטנט from Application<br>No. ..... מס'<br>dated ..... מיום | • לבקשה/לפטנט to Patent/Appl.<br>No. ..... מס'<br>dated ..... מיום |

• ייפוי כח: כללי / מיוחד — רצוף בזה / עוד יוגש
P.O.A.: general / individual-attached / to be filed later-

filed in case 99756 הוגש בענין

הסען לכתובת מסמכים בישראל
Address for Service in Israel

WOLFF, BREGMAN AND GOLLER
P.O. Box 1352
Jerusalem 91013

חתימת המבקש
Signature of Applicant

WOLFF, BREGMAN AND GOLLER

by: G. Golly

• דרישה דין קדימה
Priority Claim

| מדינת האגוד Convention Country | תאריך Date | מספר/סימן Number/Mark |
|---|---|---|
| | | |

היום 11 בחודש 5 שנת 1994
This ..... of ..... of the year .....

לשימוש הלשכה
For Office Use

# תהליך לייצור אנדרוסטיין-17-קרבוטיאואטים
# ואנדרוסטיין-17-קרבוטיאואטים המיוצרים ע"י התהליך האמור

# PROCESS FOR THE MANUFACTURE OF ANDROSTANE-17-CARBOTHIOATES AND ANDROSTANE-17-CARBOTHIOATES PREPARED THEREBY

The present invention relates to a novel and advantageous process for the manufacture of androstane-17-carbothioates.

Androstane-17-carbothioates are well known in the literature.

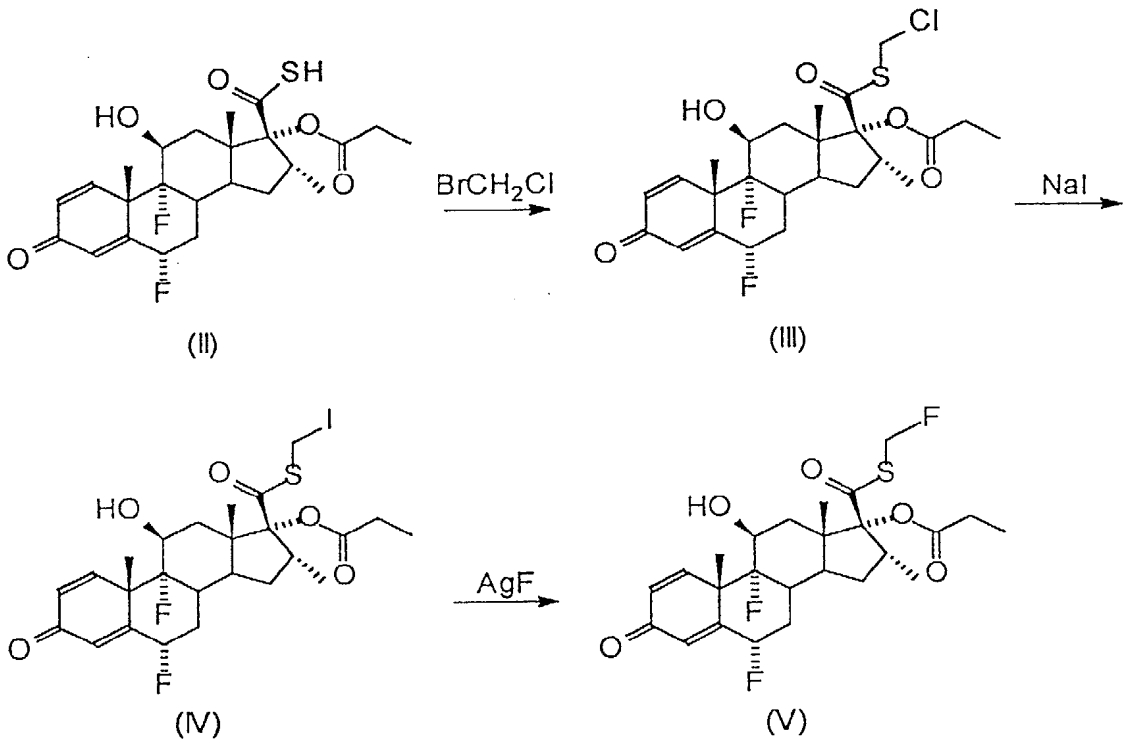
Thus, a family of such products was already described in US patents 4,188,385 and 4,198,403 to Syntex.

Recently, this family of products has achieved wide recognition and interest due to the discovery of the anti-inflammatory and anti-asthma drugs Fluticasone (6,9-difluoro-11β,17-dihydroxy-16-methyl-3-oxo- androsta-1,4-diene-17β-5-fluoromethyl ester) and its derivatives by Glaxo.

Fluticasone and other related androstane-17-carbothioates were described in British patents 2,088,877 and 2,137,206 to Glaxo Ltd.

The synthesis of androstane-17-carbothioates, as described in British patent 2,088,877, follows a lengthy and inefficient path, exemplified in Scheme 1 for Fluticasone propionate.

Scheme 1

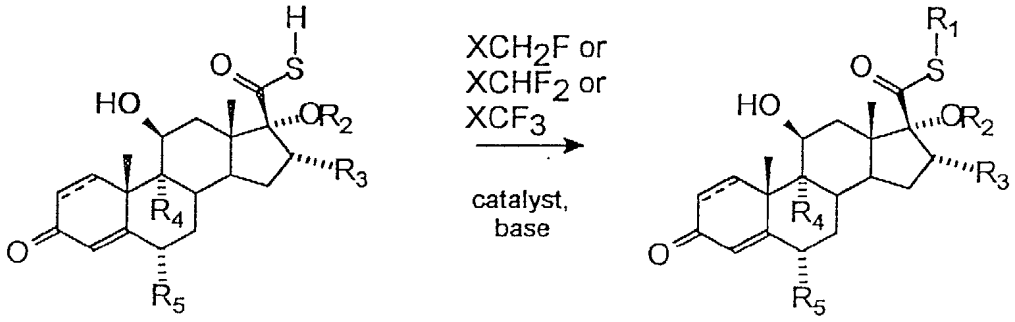



**FLUTICASONE PROPIONATE**

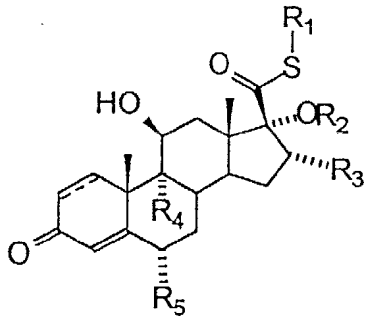
The use of silver salts and the numerous steps for the conversion of the androstane-17-carbothioic acids to their fluoromethyl esters renders the manufacture expensive, tedious and inefficient.

It has now been surprisingly found, that this synthesis can be achieved in a much simpler way, by the direct esterification of the androstane-17-carbothioic acids with a halofluoromethane of general formula $XCH_2F$, $XCHF_2$ or $XCF_3$ wherein X=Cl or Br, to achieve the desired ester in one simple step (see Scheme 2).

Scheme 2




Thus, the present invention provides a process for the preparation of an androstane-17-carbothioic ester of general formula I




(I)

wherein $R_1$ is a fluoromethyl, difluoromethyl or trifluoromethyl group,

$R_2$ represents a group $COR_6$ wherein $R_6$ is a $C_{1-3}$ alkyl group;

$R_3$ represents a hydrogen atom; a methyl group, which may be in either the $\alpha$ or ß-configuration; or a methylene group;

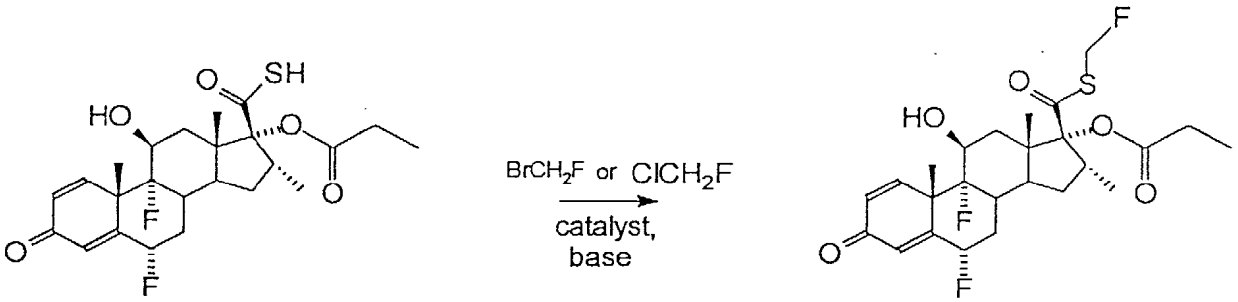
$R_4$ represents a hydrogen, chlorine or fluorine atom;

$R_5$ represents a hydrogen or fluorine atom and the symbol ..... represents a single or double bond.

by the direct esterification of a corresponding androstane-17-carbothioic acid of formula I wherein $R_1$=H with a halofluoromethane of formula $XCH_2F$, $XCHF_2$ or $XCF_3$, wherein X = Br or Cl, and optionally in the presence of a catalyst.

The new process is exemplified in Scheme 3 which describes the synthesis of Fluticasone propionate, using as halofluoromethane bromofluoromethane or chlorofluoromethane.

Scheme 3




FLUTICASONE PROPIONATE

The synthesis of androstane-17-carbothioic esters by the one-stage esterification of the androstane-17-carbothioic acids with bromofluoromethane or chlorofluoromethane was heretofore unknown.

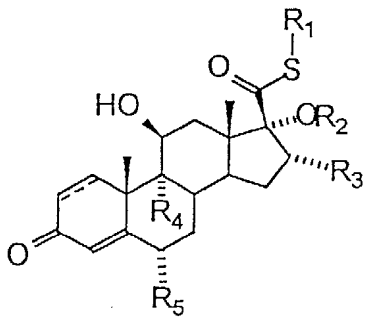
A remotely related synthesis of 4-thioandrostane-ethers was described by Roussel-Uclaf in European Patent 0375559.

The aforementioned patent does not describe the synthesis of androstane-17-carbothioates or the use of chlorofluoromethane, but only of the bromofluoromethane. Also, the syntheses described are etherifications and not esterifications, and therefore the compounds obtained are ethers and not esters.

The reaction between the androstane-17-carbothioic acids and the

halofluoromethane is preferably effected in basic medium and can be enhanced by the presence of catalysts such as phase-transfer catalysts.

The present invention also provides for an androstane-17-carbothioic ester of general formula I




(I)

wherein $R_1$ is a fluoromethyl, difluoromethyl or trifluoromethyl group,

$R_2$ represents a group $COR_6$ wherein $R_6$ is a $C_{1-3}$ alkyl group;

$R_3$ represents a hydrogen atom; a methyl group, which may be in either the $\alpha$ or ß-configuration; or a methylene group;

$R_4$ represents a hydrogen, chlorine or fluorine atom;

$R_5$ represents a hydrogen or fluorine atom and the symbol ..... represents a single or double bond,

whenever prepared by the direct esterification of a corresponding androstane-17-carbothioic acid of formula I wherein $R_1$=H with a halofluoromethane of formula $XCH_2F$, $XCHF_2$ or $XCF_3$, wherein X = Br or Cl, and optionally in the presence of a catalyst.

In a specially preferred embodiment, the present invention provides also for Fluticasone and Fluticasone propionate, whenever prepared by the direct esterification of a corresponding androstane-17-carbothioic acid of formula I wherein $R_1$=H with bromofluoromethane or chlorofluoromethane, and optionally in the presence of a catalyst.

While the invention will be now described in connection with certain preferred embodiments in the following Examples so that aspects thereof may be more fully understood and appreciated, it is not intended to limit the invention to

these particular embodiments. On the contrary, it is intended to cover all alternatives, modifications and equivalents as may be included within the scope of the invention as defined by the appended claims. Thus, the following Examples which include preferred embodiments will serve to illustrate the practice of this invention, it being understood that the particulars shown are by way of example and for purposes of illustrative discussion of preferred embodiments of the present invention only, and are presented in the cause of providing what is believed to be the most useful and readily understood description of procedures as well as of the principles and conceptual aspects of the invention.

Example 1

To 2.94 gr of 6,9 -difluoro-11β-hydroxy-16-methyl-3-oxo-17-propionyloxyandrosta-1,4-diene-17-carbothioic acid (I) in 80 ml THF at 0°C, is added 1 gr potassium tert-butylate and 0.3 gr tetrabutylammonium bromide. The mixture is stirred for 30 minutes at 0°C then heated to 30°C. A flow of bromofluoromethane diluted with nitrogen is passed through the solution for 2 hours.

Saturated ammonium chloride solution (80 ml) and dichloromethane (120 ml) are added to the reaction mixture. The resulting two-phase mixture is stirred thoroughly for 1 hour, then the dichloromethane layer is separated, dried on $MgSO_4$ and evaporated to dryness.

The crude product is purified by chromatography on silica eluted with ethyl acetate:hexane (3:7). The pure fractions are evaporated to dryness, dissolved in dichloromethane, the solution is treated with carbon black and evaporated to dryness. The crystalline residue (yellow oil, 650 mg) is recrystallised from ethyl acetate to afford 450 mg of Fluticasone propionate.

Example 2

To 2.94 gr of 6,9 -difluoro-11β-hydroxy-16-methyl-3-oxo-17-propionyloxyandrosta-1,4-diene-17-carbothioic acid (I) in 80 ml THF at 0°C, is added 1 gr potassium tert-butylate and 0.5 gr benzyl-triethylammonium chloride.

The mixture is stirred for 30 minutes at 0°C then it is charged to a pressure vessel rated at 200 atm. The vessel is filled with chlorofluoromethane at 15 atm and heated at 100°C for 3 hours, then it is cooled, the pressure released and the solution is treated with saturated ammonium chloride solution (80 ml) and dichloromethane (120 ml).

The resulting two-phase mixture is stirred thoroughly for 1 hour, then the dichloromethane layer is separated, dried on $MgSO_4$ and evaporated to dryness. The crude product is purified by chromatography on silica eluted with ethyl acetate:hexane (3:7). The fractions are evaporated to dryness, dissolved in dichloromethane, the solution is treated with carbon black and evaporated to dryness. The crystalline residue (yellow oil, 590 mg) is recrystallised from ethyl acetate to afford 430 mg of Fluticasone propionate.

Example 3

To 2.94 gr of 6,9 -difluoro-11β-hydroxy-16-methyl-3-oxo-17-propionyloxyandrosta-1,4-diene-17-carbothioic acid (I) in 80 ml THF at 0°C, is added 1 gr potassium tert-butylate and 0.5 gr tetrabutylammonium bromide.

The mixture is stirred for 30 minutes at 0°C then heated to 50°C. A flow of chlorofluoromethane diluted with nitrogen is passed through the solution for 10 hours.

Saturated ammonium chloride solution (80 ml) and dichloromethane (120 ml) are added to the reaction mixture. The resulting two-phase mixture is stirred thoroughly for one hour, then the dichloromethane layer is separated, dried on $MgSO_4$ and evaporated to dryness.

The crude product is purified by chromatography on silica eluted with ethyl acetate:hexane (3:7). The fractions are evaporated to dryness, dissolved in dichloromethane, the solution is treated with carbon black and evaporated to dryness. The crystalline residue (yellow oil, 520 mg) is recrystallised from ethyl acetate to afford 420 mg of Fluticasone propionate.

Example 4

To 2.94 gr of 6,9 -difluoro-11β-hydroxy-16-methyl-3-oxo-17-propionyloxyandrosta-1,4-diene-17-carbothioic acid (I) in 80 ml THF at 0°C, is added 1 gr potassium tert-butylate and 0.3 gr tetrabutylammonium bromide.

The mixture is stirred for 30 minutes at 0°C then it is charged to a pressure vessel rated at 200 atm. The vessel is filled with bromofluoromethane at 15 atm and heated at 100°C for 2 hours, then it is cooled, the pressure released and the solution is treated with saturated ammonium chloride solution (80 ml) and dichloromethane (120 ml).

The resulting two-phase mixture is stirred thoroughly for 1 hour, then the dichloromethane layer is separated, dried on $MgSO_4$ and evaporated to

dryness. The crude product is purified by chromatography on silica eluted with ethyl acetate:hexane (3:7). The fractions are evaporated to dryness, dissolved in dichloromethane, the solution is treated with carbon black and evaporated to dryness. The crystalline residue (yellow oil, 470 mg) is recrystallised from ethyl acetate to afford 380 mg of Fluticasone propionate.

Example 5

To 2.94 gr of 6,9 -difluoro-11β-hydroxy-16-methyl-3-oxo-17-propionyloxyandrosta-1,4-diene-17-carbothioic acid (I) in 80 ml THF at 0°C, is added 1 gr potassium tert-butylate.

The mixture is stirred for 30 minutes at 0°C then it is charged to a pressure vessel rated at 200 atm. The vessel is filled with tetrabutylamine at 15 atm and heated at 100°C for 2 hours, then it is cooled, the pressure released and the solution is treated with saturated ammonium chloride solution (80 ml) and dichloromethane (120 ml).

The resulting two-phase mixture is stirred thoroughly for 1 hour, then the dichloromethane layer is separated, dried on $MgSO_4$ and evaporated to dryness. The crude product is purified by chromatography on silica eluted with ethyl acetate:hexane (3:7). The fractions are evaporated to dryness, dissolved in dichloromethane, the solution is treated with carbon black and evaporated to dryness. The crystalline residue (yellow oil, 350 mg) is recrystallised from ethyl acetate to afford 280 mg of Fluticasone propionate.

Example 6

To 2.94 gr of 6,9 -difluoro-11β-hydroxy-16-methyl-3-oxo-17-propionyloxyandrosta-1,4-diene-17-carbothioic acid (I) in 80 ml THF at 0°C, is added 1 gr potassium tert-butylate and 0.3 gr tetrabutylammonium bromide.

The mixture is stirred for 30 minutes at 0°C then it is charged to a pressure vessel rated at 200 atm. The vessel is filled with bromotrifluoromethane at 15 atm and heated at 100°C for 2 hours, then it is cooled, the pressure released and the solution is treated with saturated ammonium chloride solution (80 ml) and dichloromethane (120 ml).

The resulting two-phase mixture is stirred thoroughly for 1 hour, then the dichloromethane layer is separated, dried on $MgSO_4$ and evaporated to dryness. The crude product is purified by chromatography on silica eluted with ethyl acetate:hexane (3:7). The fractions are evaporated to dryness,

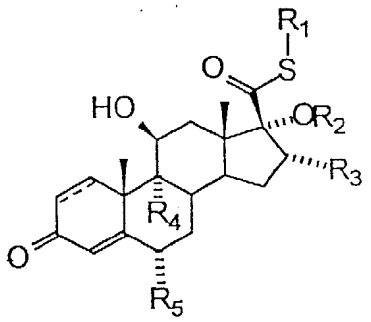
dissolved in dichloromethane, the solution is treated with carbon black and evaporated to dryness. The crystalline residue (yellow oil, 420 mg) is recrystallised from ethyl acetate to afford 340 mg of trifluoromethyl-6,9-difluoro-11β-hydroxy-16-methyl-3-oxo-17-propionyloxyandrosta-1,4-diene-17-carbothioate.

It will be evident to those skilled in the art that the invention is not limited to the details of the foregoing illustrative examples and that the present invention may be embodied in other specific forms without departing from the essential attributes therof, and it is therefore desired that the present embodiments and examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing description, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

**Claims**:

What we claim is:

1. A process for the preparation of an androstane-17-carbothioic ester of general formula I




(I)

wherein $R_1$ is a fluoromethyl, difluoromethyl or trifluoromethyl group,

$R_2$ represents a group $COR_6$ wherein $R_6$ is a $C_{1-3}$ alkyl group;

$R_3$ represents a hydrogen atom; a methyl group, which may be in either the $\alpha$ or ß-configuration; or a methylene group;

$R_4$ represents a hydrogen, chlorine or fluorine atom;

$R_5$ represents a hydrogen or fluorine atom and the symbol ..... represents a single or double bond.

by the direct esterification of a corresponding androstane-17-carbothioic acid of formula I wherein $R_1$=H with a halofluoromethane of formula $XCH_2F$, $XCHF_2$ or $XCF_3$, wherein X = Br or Cl, and optionally in the presence of a catalyst.

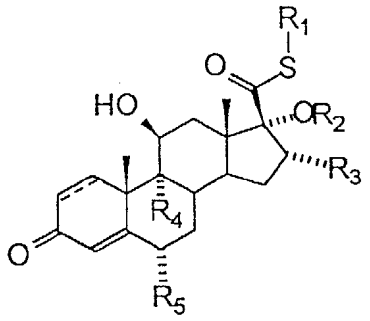
2. A process for the synthesis of an androstane-17-carbothioate ester as defined in Claim 1, wherein $R_1$ is $-CH_2F$, by reaction of an androstane-17-carbothioic acid of formula I wherein $R_1$=H with bromofluoromethane or chlorofluoromethane, and optionally in the presence of a catalyst.

3. A process for the synthesis of androstane-17-carbothioate esters as described in Claim 1 where $R_1$ is a polyfluoromethyl group of formula $-CF_3$ or $-CHF_2$, by the reaction of androstane-17-carbothioic acids with a halofluoromethane of formula $XCF_3$ or $XCHF_2$, wherein X=Cl or Br.

4. A process as defined in Claim 1, wherein the process is performed under a pressure of 1-100 atm.

5. A process as defined in Claim 1, wherein the catalyst is a phase-transfer catalyst.

6. An androstane-17-carbothioic ester of general formula I




(I)

wherein $R_1$ is a fluoromethyl, difluoromethyl or trifluoromethyl group,

$R_2$ represents a group $COR_6$ wherein $R_6$ is a $C_{1-3}$ alkyl group;

$R_3$ represents a hydrogen atom; a methyl group, which may be in either the $\alpha$ or ß-configuration; or a methylene group;

$R_4$ represents a hydrogen, chlorine or fluorine atom;

$R_5$ represents a hydrogen or fluorine atom and the symbol ..... represents a single or double bond. whenever prepared by the process of Claim 1.

7. Fluticasone, whenever prepared by the process of Claim 1.

8. Fluticasone propionate, whenever prepared by the process of Claim 1.

For the Applicant
WOLFF, BREGMAN AND GOLLER
by: G Goller